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RAE-VENTER LAW GROUP P.C.
PO Box 60039
Palo Alto, CA 94306

EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1633	11

DATE MAILED: 12/06/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/403,213	Applicant(s) NOTEBORN ET AL.	
	Examiner Brian Whiteman	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Letter* .

DETAILED ACTION

Non-Final Rejection

A non-compliance letter was sent on 9/28/01 paper no. 10. The examiner has withdrawn paper no. 10 and instead added the sequence to compliance letter with this office action. Thus, kindly disregard the sequence to comply letter in paper no. 10 filed on 9/28/01 for it is now void and reply to the sequence to comply letter enclosed in the non-final rejection set forth in paper no. 10.

1. **Noncompliance**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CAR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CAR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CAR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply (see paper no. 10) with the reply.

Priority

This application is a 371 of PCT/NL98/00213 filed on 4/15/1998 is acknowledged. The EPO 97201121.7 filed on 4/15/97 and EP 97203595.0 filed on 11/15/97 are acknowledged under 35 USC 119 (a-d).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information

submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

International Search Report was submitted with the PCT/NL98/00213 and the report is acknowledged.

The amendment filed on 4/27/01 paper no. 7 is acknowledged and claims 6, 7, 10, 12, 14, 17, 19, and 20 have been amended in paper no. 7.

Claim Objections

Claims 2, 12, 16, 19, and 21 are objected to because of the following informalities: Claim 2 should read, "A gene delivery vehicle according to claim 1 additionally comprising a modified translation initiation site directly upstream of the ATG-initiation codon of said nucleic acid molecule." Claim 12 is missing a period at the end of the claim. Claims 16, 19, and 21 are missing a comma before the word "and." Claim 16 should read, "HEK-293, HER-911, PER-C6, Psi-2, and PA-317 cells." A claim cannot have two periods in the claim (e.g. PER.C6. Appropriate correction is required.

Claims 1-21 are pending for examination.

In view of the compact composition, the claims (17-21) beginning with the term "use" will be assumed to be a method of using the gene delivery vector. Should applicant amend the claims, so that the claims no longer resemble the original claims, a restriction may be necessary.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 as best understood, are readable on a genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein, wherein the genus of is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 3, 5, 6, and 7 as best understood, are readable on a genus of a modified translation initiation site directly upstream the ATG-initiation codon of said chicken protein(s), wherein the genus of a modified translation initiation site is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates using a nucleic acid molecule encoding apoptin-like activity protein and/or a VP2-like activity protein for making a gene delivery vector. The specification coupled with the state of the art provides sufficient description of the chicken protein VP3 and sufficient description of the chicken protein VP2 as disclosed in the Noteborn et al., WO 95/03414. However, it is apparent that on the basis of applicant's disclosure, an

adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein that must exhibit the disclosed biological functions as contemplated by the claims.

The as-filed specification contemplates a modified translation initiation site directly upstream of the ATG-initiation codon. The specification provides sufficient description of the nucleic acid 5'-GCCAAC-3' (page 19). However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a nucleic acid sequence that can inserted upstream of the ATG-initiation codon to increase the synthesis of apoptin as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a genus of a nucleic acid molecule sequence that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid

molecule encoding a VP2-like activity protein. In addition, it is not sufficient to support the present claimed invention directed to a genus of a modified translation initiation site directly upstream of the ATG-initiation codon of said chicken protein. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a nucleic acid molecule encoding an apoptin-like activity protein, a genus of a modified translation initiation site directly upstream of the ATG-initiation codon of said chicken protein, and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein or a genus of a modified translation initiation site directly upstream of the ATG-initiation codon of said chicken protein that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of

the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A gene delivery vector comprising a nucleic acid sequence encoding a chicken VP3 protein; 2) A gene delivery vector comprising a nucleic acid sequence encoding a chicken VP2 protein; 3) The gene delivery vector of 1, further comprising a nucleic acid sequence encoding a chicken VP2 protein; 4) The gene delivery vector of 3, further comprising at least one target molecule, wherein the target molecule is reactive with a tumor cell surface receptor; 5) A host cell comprising the gene delivery vector of 4; 6) A method for inducing apoptosis in a mammalian tumor by directly administering to the tumor the gene delivery vector of 4, 7) The method of 6 further comprising using chemotherapy, 8) The gene delivery vector of 1 or 2 additionally comprising of a modified translation initiation site directly upstream from the ATG-initiation codon of said chicken VP2 and/or said chicken VP 3 protein, wherein the nucleic acid sequence is GCCAAC; and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a genus of a nucleic acid molecule encoding an apoptin-like activity protein and/or a genus of a nucleic acid molecule encoding a VP2-like activity protein), particularly in view of the reasons set forth above, one skilled in the art would not have

known how to use and make the claimed invention so that it would operate as intended, e.g.. function in a gene delivery carrier for use in a method of inducing apoptosis in tumor cells.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention lies in a gene delivery carrier used in a method of cancer gene therapy or in an in vitro method of diagnosis cancerous cells.

Furthermore, and with respect to claims 17-19 directed to any virus and/or replicant defective viruses useful for gene therapy and directed to any therapeutic treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, at the time the application was filed gene therapy was considered unpredictable.

The specification provides working examples: The construction of recombinant vector comprising a nucleic acid encoding the chicken VP3 protein and using several packaging and helper cell lines (pages 8-16). On page 17, the disclosure examined whether the construct would induce apoptosis in isolated cell cultures comprising human transformed (page, 17, lines 19-20)

and/or malignant cell lines (line 23). The construct exhibited apoptosis in different mammalian tumorigenic and transformed cell lines (Fig 4). On page 18 displays the construct did not induce apoptosis in an isolated culture of normal non-transformed human cells. On page 19 the disclosure examined the effect of incorporating a nucleic acid sequence in front of the ATG-initiation codon for the chicken VP3 protein. The result is 5 times more VP3 expression compared to the original direct upstream sequence. On page 20, the disclosure co-expresses two vectors (one vector comprising the chicken VP2 protein and the other vector comprising the chicken VP 3 protein) in an isolated culture of Saos-2 cells. The results in Figure 5 show that VP2 enhances the apoptosis. The disclosure produces a retrovirus vector expressing VP3 and showed that the vector can induce apoptosis in an isolated culture of human tumor cells (pages 21-22). On page 23, the disclosure prophetically contemplates how a diagnostic assay comprising rAD-VP3 would function. On pages 23-26, the specification determined toxicity in experimental rats by intravenously, intra-peritoneally, or subcutaneously injection. The results showed that the expression of VP3 has not toxic effect in vivo. On pages 26-29, the disclosure used nude mice and injected subcutaneously into the nude mice tumorigenic cells and after the tumors developed, the specification intra-tumorally injected rAd-VP3 and control rAD-con1 vectors into the tumors. The results showed that the tumors injected with rAD-VP3 vector were reduce in sized compared to the tumors injected with the control vector.

The disclosure provides sufficient guidance for how these experiments reasonably correlate to an in vivo method of gene therapy for treating tumor cells in any mammal except humans comprising intra-tumoral administration to said mammal with a recombinant replicant defective vector. In addition, the as-filed specification is enabled for the treatment listed above

further comprising using chemotherapy. However, these experiments do not reasonably correlate to any other in vivo method of gene therapy for treating any other type of cancer cell using intravenous, intraperitoneal, dermal, nasal, buccal, rectal, vaginal or topical administration of recombinant vector comprising a nucleic acid sequence encoding VP2 and VP3.

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> Vile further discusses:
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor

cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In view of the concerns set forth by the state of the art, the as-filed specification does not reasonably address the concerns put forth by the state of the art for cancer gene therapy. In addition, in further view of reasons set forth above and the lack of written description for any apoptin-like activity or any VP2 like activity other than the VP2 and the VP3 protein described in the specification, it is not apparent to one skilled in the art how to reasonably extrapolate experiments comprising an adenovirus replicant defective vector used to inhibit or kill tumor cells to any other apoptin-like activity protein up to and VP2-like activity protein [*e.g.* the as-filed specification does not describe any SEQ ID NOs encoding the VP2 or VP3 protein]. Furthermore, because of the lack of guidance, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (*e.g.*, see Chiu et al., *Folding and Design*, Vol. 3, pp. 223-228, 1998), it would require an undue amount of extended experimentation to determine which apoptin-like activity and VP2-like activity other than the VP2 and VP3 described in the specification would function for an anti-cancer effect. With the reasons set forth above it would require undue experimentation to identify other nucleic acid molecules having either apoptin-like activity or VP2-like activity.

Furthermore, in view of any claim encompassing using any gene delivery encoding VP2 and VP3. The as-filed specification is only enabled for replicant defective adenovirus or retrovirus. The state of the art for using any vector in anti-cancer gene therapy as exemplified by Vile et al., *Gene Therapy*, Vol. 7, pp. 3, 2000. Vile teaches:

> To date, cancer gene therapy trials have variously used the three most common vectors (plasmid, retrovirus, and adenovirus). However, except for the situation where tumor/immune cells are manipulated ex vivo, there will be a clear preference in the coming years for the use of adenoviral vector for in vivo delivery to tumors. Dominant (10^{11} p.f.u./ml) compared with other vectors. The initial rationale of the use of C-type retroviral vectors to target exclusively dividing tumor cells on the background of a quiescent tissue is being gradually superseded by the realization that human tumors generally cycle much more slowly than the rodent cell lines on which the strategy was based.
>
> However, even the highest titer system is clearly not high enough yet to cure even local tumors. Therefore, there is a clear need to explore and exploit, a range of alternative options. Other systems, such as AAV and HSV, are already well developed for use in other gene therapy contexts and may be valuable in certain conditions within the cancer area.
>
> The development of replication vectors for cancer gene therapy is the inevitable consequence of data from the early clinical trials. So far, a substantial therapeutic gap still exists between the overlap of the efficacy provided by, on the other hand, the potency of the therapeutic gene(s) and on the other, the efficiency of gene delivery

provided by the vector. Only when these two 'therapeutic domains' approach each other will clinical efficacy result.

In addition, the applicants claim a viral composition comprising a recombinant (*e.g.* replicant and/or replicant defective viral vector) vector, wherein said vector is any viral vector encoding a VP3 and VP2 proteins. It is not apparent to one skilled in the art how using a retroviral, adenovirus replicant defective vector reasonably correlates to using any other gene delivery carrier (e.g. ligand, steroid, metal). One skilled in the art cannot reasonably extrapolate from using an in vitro experiment showing co-transfection of to administering any other gene delivery carrier to a tumor in a mammal. Also, the as-field specification does not address the concern with repeated administration of an immunogenic vector since repeated administration would cause decrease expression of the desired anti-cancer protein. In view of the state of the art for using several types of gene delivery carriers for treating cancer in a subject, it would take one skilled in the art an undue amount of experimentation to determine how to use any gene delivery composition other than the replicant defective adenovirus or retrovirus to treat cancer in a mammal.

Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in a therapeutic response using the recombinant replicant defective vector comprising nucleic acid sequences encoding the chicken VP3 and VP2 proteins. The specification displays that VP3 reduces tumor size in nude mice by direct administration of the replicant defective adenovirus. The state of the art for the route of administration for gene therapy as exemplified by Verma,

Nature, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In view of the state of the art, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any other route of administration to generate a therapeutic response in any subject with cancer.

Furthermore with respect to claims 1-3, 5, and 7, which encompass the gene delivery vector, wherein said vector additionally comprises a modified translation initiation site directly upstream from the ATG-initiation codon of the chicken VP2 protein and/or the chickenVP3 protein, the disclosure does not provide sufficient guidance the genus of modified translation initiation sites that would increase the expression of said chicken proteins. The specification lacks sufficient guidance, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (*e.g.*, see Chiu et al., *Folding and Design*, Vol. 3, pp. 223-228, 1998), it would require an undue amount of extended experimentation to determine which modified translation initiation site other than the nucleic acid sequence GCCAAC described in the specification that would function as contemplated in the claimed embodiment. With the reasons set forth above it would require an undue experimentation to identify other nucleic acid sequences that must exhibit the disclosed biological functions as contemplated by the specification (e.g. increase the expression of the chicken VP3 protein) other than the nucleic acid sequence 5'-GCCAAC-3'.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed virus or replicant viruses generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy methods as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

At best the disclosure is enabled for 1) A gene delivery vector comprising a nucleic acid sequence encoding a chicken VP3 protein; 2) A gene delivery vector comprising a nucleic acid sequence encoding a chicken VP2 protein; 3) The gene delivery vector of 1, further comprising a nucleic acid sequence encoding a chicken VP2 protein; 4) The gene delivery vector of 3, further comprising at least one target molecule, wherein the target molecule is reactive with a tumor cell surface receptor; 5) A host cell comprising the gene delivery vector of 4; 6) A method for inducing apoptosis in a mammalian tumor by directly administering to the tumor the gene delivery vector of 4, 7) The method of 6 further comprising using chemotherapy, 8) The gene delivery vector of 1 or 2 additionally comprising of a modified translation initiation site directly upstream from the ATG-initiation codon of said chicken VP2 and/or said chicken VP 3 protein, wherein the nucleic acid sequence is 5'-GCCAAC-3'.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable for 1-8, listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable after the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any

gene delivery carrier cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "VP2-like activity" in claims 4-21 is a relative term, which renders the claim indefinite. The term "VP2-like activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. Clarification is requested.

Claims 2, 3, 5, and 7 are vague and indefinite as to what is intended to be encompass with regard to a the vector system of claim 1, which additionally comprises a modified translation initiation site directly upstream the ATG-initiation codon. The disclosure does not define the metes and bounds of the claims. It is not apparent in view of the disclosure how the modified translation site is operatively linked to the gene delivery vector of the claims. Suggest supplying a figure for the vector pCR-Vp3mu displaying exactly where upstream the nucleic acid sequence 5'-GCCAAC-3' is located.

The term "apoptin-like activity" in claims 1-3 and 6-21 is a relative term, which renders the claim indefinite. The term "apoptin-like activity" is not defined by the claim, the

specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. Clarification is requested.

The statement in claims 2-14 and 17-21, **a** gene delivery vehicle according to claim " is indefinite because it does not point out which vehicle **a** gene delivery vehicle is referring to in the claims. The dependent claims should state "**The** gene delivery vehicle according to claim."

Claim 12 is vague and indefinite as to what is intended to be encompass with regard to a the vector system of claim 1, which additionally comprises at least one target molecule. The disclosure does not define the metes and bounds of the claim. It is not apparent in view of the disclosure how the target molecule is operatively linked to the gene delivery carrier of claim 1.

The statement in claims 15-16, "**A** host cell according to claim 14" is indefinite because it does not point out which cell **A** host cell is referring to in the claims. The dependent claims should state "**The** host cell according to claim 14."

Claims 17-21 provides for the use of a gene delivery vehicle according to claim 13, 17, or 20, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 17-21 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 4, 6, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Noteborn et al. (WO 95/03414). Noteborn teaches that VP1, VP2, and VP3 were expressed into baculovirus system separately or in combination with one or two other CAV proteins an can be used for tracing antibodies directed against CAV (page 7, lines 12-15). Furthermore, Noteborn teaches that VP2 together with VP3 can induce cell death in tumor cells (page 8, lines 30-32 and page 28 line 7- page 30 line 8 and page 38, claim 25). Noteborn further teaches that the construct pRSV-VP3 contained the coding region for VP3 under regulation of the Rous sarcoma virus (page 25, lines 26-28). Thus, Noteborn anticipates a gene delivery vector comprising a nucleic acid sequence molecule encoding the chicken VP3 and/or VP2 proteins.

Claims 1, 4, 6, 8, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Noteborn et al. (US Patent No. 5,981,502, effective filing date 6/7/1995). Noteborn teaches an expression cassette comprising a regulatory region for control of transcription and/or translation operably linked to nucleic acid encoding a chicken VP3 receptor ligand and/or chicken VP2 receptor ligand (column 6, lines 7-11). Furthermore, Noteborn teaches that the expression cassette is included in a vector; generally a plasmid or it can be in a phage, which has a

transcriptional regulatory sequence providing for the desired transcriptional activity (column 6, lines 17-19). One skilled in the art would anticipate that phage reads on gene delivery vector that is a virus and that it is a replication-defective virus. Thus, Noteborn anticipates a gene delivery vector comprising a nucleic acid sequence molecule encoding VP3 and/or VP2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 8, 9, 11, 12, 13, 14, 17, and 19, are rejected under 35 U.S.C. 103(a) as being unpatentable over Noteborn et al. (US Patent 6,162, 461, effective filing date 6/7/95) taken with Zuckermann et al (US Patent No. 6,251,433, effective filing date 8/13/96). Noteborn teaches a method for inducing tumor cell death by directly introducing into said tumor cells a DNA molecule coding for one or both polypeptide depicted in Fig. 2 (SEQ ID NO: 5) or Fig 3 (SEQ ID NO: 7), under conditions whereby said cells express said DNA, whereby death in said tumor cells is induced, wherein said introducing of said DNA into said tumor cells is via a viral vector (column 26, lines 1-26 and column 48, claims 31 and 32). SEQ ID NO: 5 is the DNA sequence for the chicken VP2 protein and SEQ ID NO: 7 is the DNA sequence for the chicken VP 3 protein (column 3, lines 40-48). Furthermore, Noteborn teaches that the expression of VP3 can be used for the induction of cell death in human tumors by means of DNA transfection in vitro. Expression of VP3 in tumor cells may also take place by infecting cells with retroviral vectors (column 6, lines 32-36). Furthermore, it was well known to one skilled in the art of cancer gene therapy at the time the invention was made that when either the VP3 protein and/or the VP2 protein are expressed in host cells, they induce apoptosis in tumor cells and not in normal cells. However, Noteborn does not teach a gene delivery vector which additionally comprises a target molecule, which is reactive with a tumor cell surface.

However, at the time the invention was made, Zuckermann teaches compositions and methods for increasing the uptake of polynucleotides into cells by using additional agents for helping the endocytosis of the vector (column 17, line 25 - column 21 line 6), wherein the polynucleotides can be vectors (column 6, lines 35-39). Furthermore, the vectors can be retroviral vectors (column 8, lines 39-44) and the vectors can used for in vitro or in vivo

applications (column 6, lines 39-40). Zuckermann teaches that the polynucleotides and methods of the invention can be utilized with any type of host cell (column 6, lines 52-53). Zuckermann further teaches that the polynucleotides can delivered to treat hyperplasia, and list several polynucleotide that could be used in method of treating hyperplasia is the apoptin gene (column 12, lines 15-20). Thus, Zuckermann produces a gene delivery vector (e.g. retroviral vector) that can use with additional agents for improving the endocytosis of the desired vector or aid in the binding of the vector to the cell surface or both.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Noteborn and Zuckermann, namely to produce a gene delivery vector comprising a polynucleotide sequence encoding either the VP3 protein and/or the VP2 protein and a target molecule for use in a method of inducing tumor cell death in a mammal by directly administering a vector to said tumor. One of ordinary skill in the art would have been motivated to employ the gene delivery vector taught by Noteborn taken with Zuckermann to increase the uptake of the vectors into cancer cells for inducing tumor cell death in a mammalian subject by directly administering the vector into said tumor.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 6, 8, 9, 10, and 12-16 are rejected under 35 U.S.C 103(a) as being patentable over Noteborn and Tuckermann taken with Fallaux et al. (US Patent No. 5994128, effective filing date 6/14/96) and Fallaux et al. (Human Gene Therapy, Vol. 7, pp. 215-22, 1996).

The rejections of the base claims 1, 6, and 12 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Noteborn taken with Tuckermann. Noteborn and Tuckermann do not teach

a gene delivery vector comprising a nucleic acid sequence encoding VP3 and a nucleic acid sequence encoding VP2, wherein the vector is a replicant defective adenovirus and host cell comprises the gene delivery vector described above.

However, at the time the invention was made, replicant defective adenoviruses were well known in the art as exemplified by Fallaux. Fallaux teaches an E1 deleted recombinant adenovirus (rAdV) and the preferred host for production of the rADV is cell line 293 (abstract). Fallaux further teaches:

> a cell line that demonstrates several characteristics in common with the well-known 293 cell line, the 911 cell line is highly transfectable and exhibits similar frequencies of homologous recombination. The 911-cell line has characteristics that make it a useful alternative for 293. The 911 cells perform well in plaque assays and the yield of rADV compared to 293 is three times as high. See abstract of journal article.

In addition, Fallaux teaches that PER.C6 can be used for packaging constructs without the need for marker gene (US Patent, column 6, lines 19-21). Fallaux further teaches that rADV are preferred vectors for gene therapy since the goal of the therapy is the expression of the therapeutic protein and not the viral proteins because the expression of viral proteins in host cells results in inflammation and recognition by cytotoxic T lymphocytes which eradicate transduced cells (US Patent, column 4, lines 4-10).

It would have been *prima facie* obvious for a person of ordinary skill in the art at the time the invention was made to combine the teaching of Noteborn and Tuckermann taken with Fallaux to produce E1 deleted recombinant adenoviruses comprising of a nucleic acid sequence encoding VP2 protein and/or a nucleic acid sequence encoding a VP3 protein with an additional

agent to increase the endocytosis of the vector. Furthermore, it would have been obvious to one of ordinary skill in the art to use 911 cells in the production of E1 deleted recombinant adenoviruses. One of ordinary skill in the art would have been motivated to employ adenovirus vectors since they are able to transfect dividing/non-dividing host cells and decrease the immunogenic host's response to the vector when administered to a mammal. In addition, one of ordinary skill in the art would have been motivated to have employed the 911 cell line since they produce three times the number of vectors compared to using 293 cells for the production of E1 deleted recombinant adenoviruses.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 6, 12, 13, 17, and 18 are rejected under 35 U.S.C 103(a) as being patentable over Noteborn and Tuckermann taken with Henderson et al. (US Patent No. 6,197,293, effective filing date 3/3/97).

The rejections of the base claim 1, 6, 12, 13, and 17 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Noteborn taken with Tuckermann. Noteborn and Tuckermann do not teach a gene delivery vector comprising a nucleic acid sequence encoding the VP3 protein and a nucleic acid sequence encoding the VP2 protein for use in a method of cancer gene therapy in combination with chemotherapy.

However, at the time the invention was made, several chemotherapy methods were well known in the art as exemplified by Henderson et al. (US Patent No. 6,197,293, column 2, line 49- column 3, line 55). Henderson teaches that a major obstacle to cancer therapy is the problem of selectivity; that is, the ability to inhibit the multiplication of tumor cells, while leaving

unaffected the function of normal cells. Thus, the therapeutic ratio, or ratio of tumor cell killing to normal cell killing of traditional tumor chemotherapy, is only 1.5:1 (column 3, lines 39-45). Thus, more effective treatment methods and pharmaceutical compositions for therapy of hyperplasia and neoplasia are needed (column 3, lines 46-47).

It would have been *prima facie* obvious for a person of ordinary skill in the art at the time the invention was made to combine the teaching of Noteborn and Tuckermann taken with Henderson to use the gene delivery carrier in method of cancer gene therapy in combination with chemotherapy. One of ordinary skill in the art would have been motivated to employ the method of cancer gene therapy in combination with chemotherapy to improve cancer treatment in a mammal since VP2 and VP3 mainly target cancerous cells and leave healthy cell alone.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1633
November 30, 2001

DAVE T. NGUYEN
PRIMARY EXAMINER

Application No.: 09/403213

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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